LB3 - Topline Results From the Phase 2 PIONEER Trial of Oral T3D-959 for the Treatment of Patients Diagnosed With Mild-to-Moderate Alzheimer's Disease

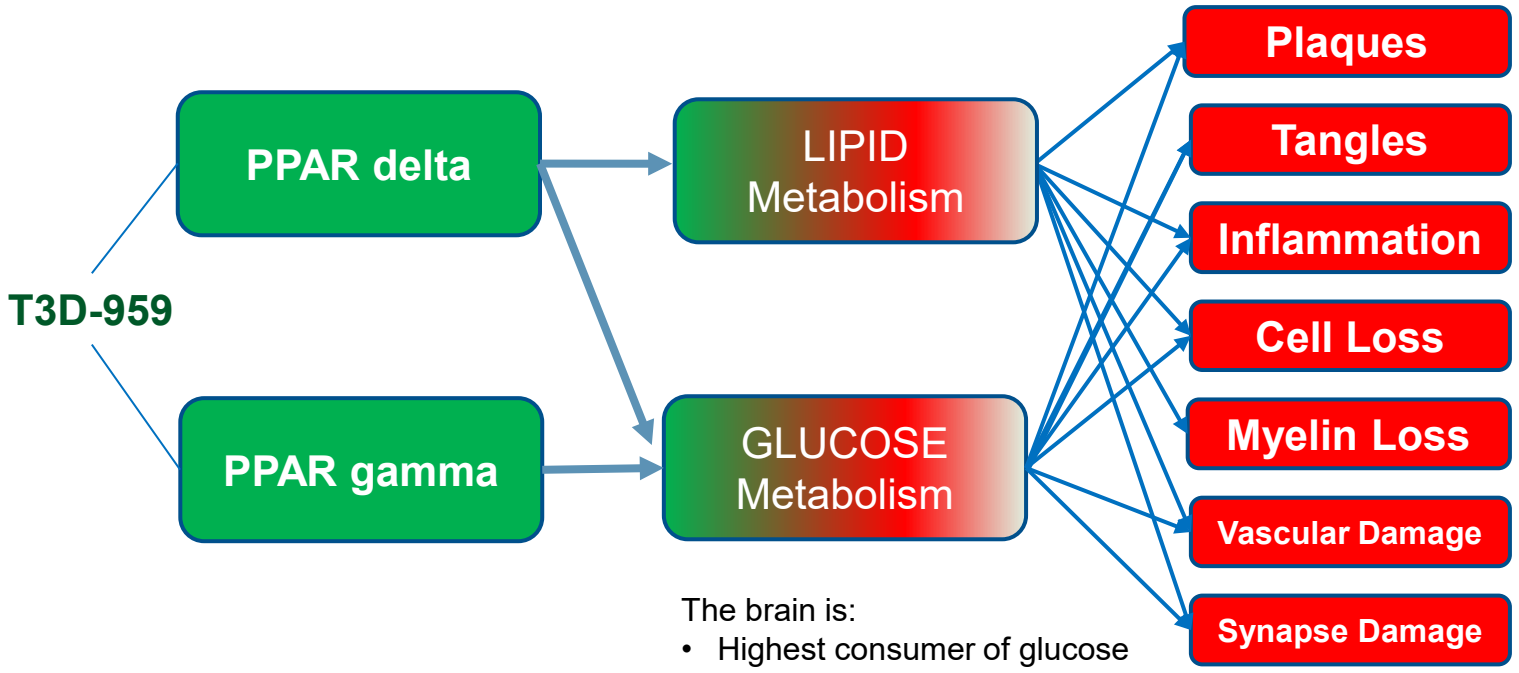
CTAD 2023

October 24, 2023

T3D-959: Mechanism of Action - General

Lead Product: Unique Dual Nuclear Receptor Agonist to Restore Brain Metabolism

- Primary Target is PPARδ (delta)
  - Secondary Target is PPARγ (gamma);
    - Regulating expression of multiple genes involved in glucose and lipid metabolism.
      - PPARδ (energy expenditure) and PPARγ (energy storage) are master regulators of metabolic homeostasis



The brain is:
- Highest consumer of glucose
- Composed of ½ lipid

T3D-959: Mechanism of Action Relationship to AD Pathologies

A. Impaired Glucose Metabolism in AD is a result of Insulin Resistance –

PPAR delta/gamma activation > ↑ Insulin receptors, ↑ IRS-1, ↑ GLP-1, ↑ AMPK, activates AKT pathway, ↑ GLUT4

B. Insulin Resistance results in:

1. Energy Blockade (mitochondrial dysfunction) –

PPAR delta/gamma activation > ↑ PGC1-α for mitochondrial biogenesis & oxidative capacity, ↑ catalase, SOD1 & glutathione

2. Altered posttranslational modifications (glycosylation, phosphorylation, ubiquitination, methylation) > ER stress > misfolded proteins that leads to:

A. Inflammation > JNK pathway activation, NFκB activation –

PPAR delta/gamma activation > ↓ JNK pathway & NFκB activation, ↓ AGEs, ↑ Adiponectin

B. Structure/Function deficiencies >Lipid Metabolism > Cholesterol forms imbalance, toxic ceramides, altered sphingolipids, decreased myelin –

PPAR delta/gamma activation > ↑ reverse cholesterol transport, ↑fatty acid oxidation & HDL, ↓ ceramides ↓ TGs, ↑ myelination

C. Amyloid Plaques

PPAR delta/gamma activation > ↓ BACE1, ↑ Neprilysin & IDE-1, ↑ ABCA1, Microglia shift to M2

D. Tau Tangles

PPAR delta/gamma activation > ↓ tau hyperphosphorylation

PIONEER Trial Design:

- A Phase 2 randomized, double-blind, placebo-controlled design clinical trial
- Evaluating three dose levels (15mg, 30mg, 45mg) of T3D-959 vs. placebo in 256 subjects (64/arm) with mild-to-moderate Alzheimer's Disease (MMSE 14-26, CDR-Global 0.5-2.0 and CDR-SB $\geq$ 3.0)
- No PET (amyloid / tau) or other biomarker entry criteria
- Subjects stratified by gender and ApoE4 genotype, assigned to one of four dose groups (1:1:1:1 ratio) in a randomized fashion
- Study medication taken orally once daily for 24 weeks
- Follow-up visit four weeks after the end of treatment
- 36 US clinical trial sites

PIONEER Trial Outcome Measures:

Primary

- Safety and Tolerability
- Cognition – ADAS-Cog11
- Function – ADCS-CGIC

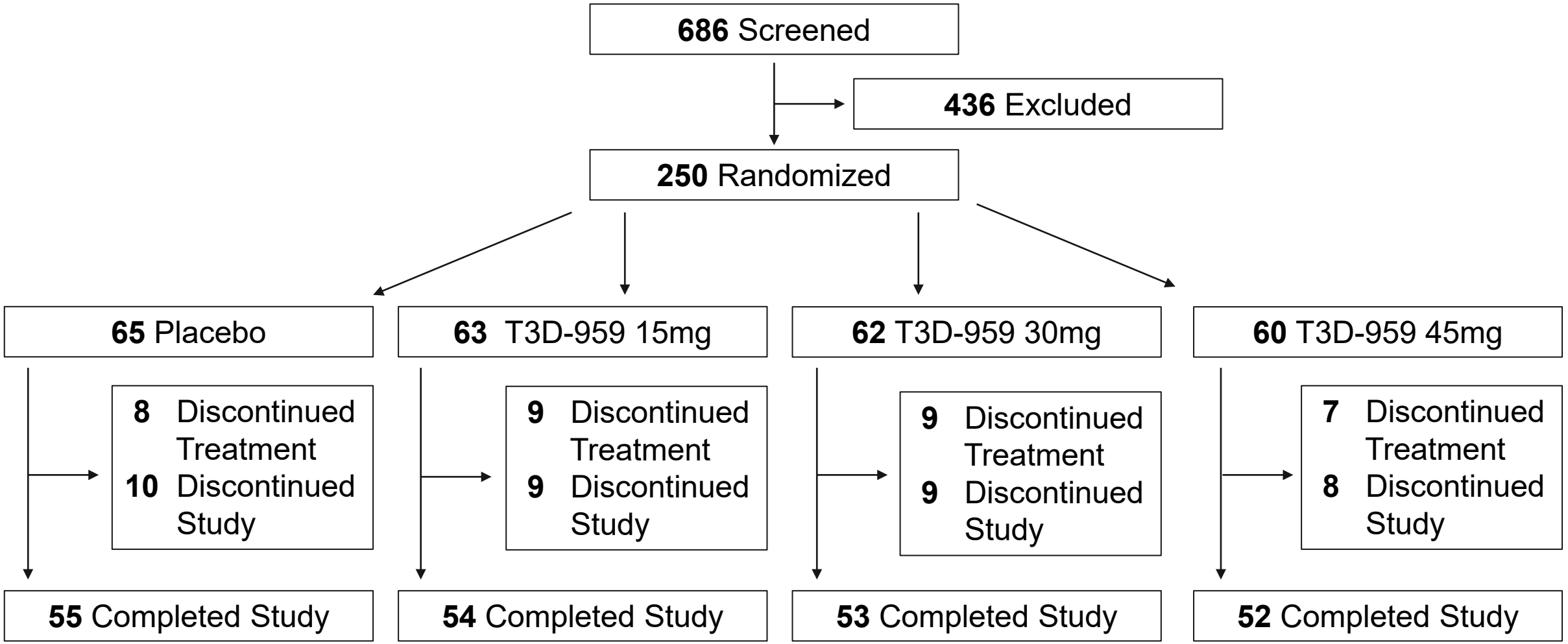
Secondary

- Amyloid Plaque Burden – Plasma Aβ42/40 ratio
- Executive Function – DSCT

Exploratory

- Blood Biomarkers – Neurodegeneration (e.g., Nfl, Neurogranin), Hyperphosphorylated Tau (e.g., pTau-217/Non-pTau-217), Inflammation, Metabolism
- Apathy – NPI
- Expressive Language – CFT
- Physical Activity – RAPA
- Brain Glucose Metabolism – FDG-PET scans

Subject Disposition

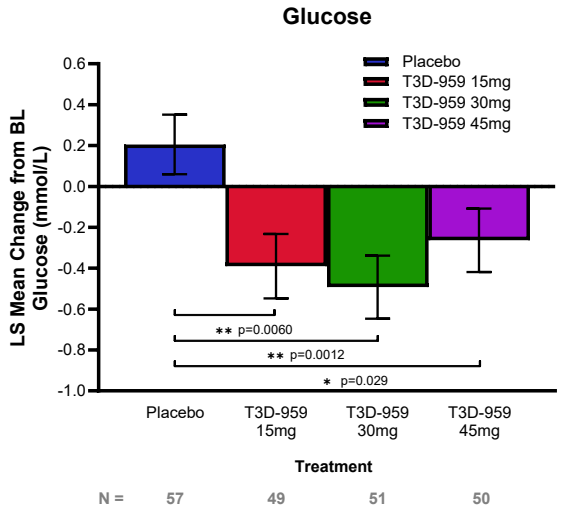


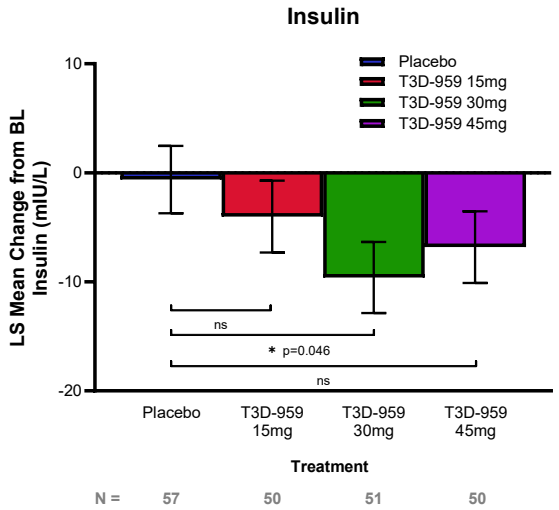
Baseline Characteristics

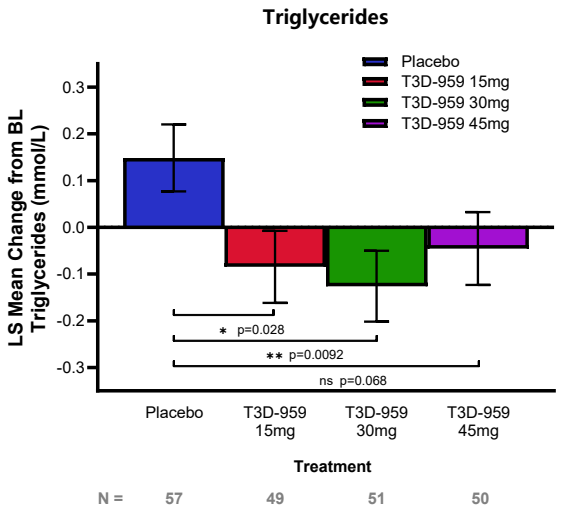
	Placebo (N=65)	T3D-959 15mg (N=63)	T3D-959 30mg (N=62)	T3D-959 45mg (N=60)
Sex				
Female, N (%)	40 (61.5)	40 (63.5)	39 (62.9)	37 (61.7)
Age (years)				
Mean (SD)	72.6 (± 8.27)	73 (± 8.31)	73.2 (± 7.17)	72.9 (± 8.29)
Min, Max	53, 90	54, 87	57, 89	51, 88
Race				
Asian, N (%)	3 (4.6)	2 (3.2)	4 (6.5)	0 (0.0)
Black/African American, N (%)	5 (7.7)	5 (7.9)	3 (4.8)	8 (13.3)
Native Hawaiian/Pacific Islander, N (%)	0 (0.0)	0 (0.0)	2 (3.2)	0 (0.0)
White, N (%)	56 (86.2)	53 (84.1)	52 (83.9)	52 (86.7)
Other, N (%)	1 (1.5)	3 (4.8)	1 (1.6)	0 (0.0)
Ethnicity				
Hispanic/Latino, N (%)	37 (56.9)	34 (54.0)	28 (45.2)	31 (51.7)
Non-Hispanic/Latino, N (%)	27 (41.5)	27 (42.9)	34 (54.8)	28 (46.7)
Not Reported or Unknown, N (%)	1 (1.5)	2 (3.2)	0 (0.0)	1 (1.7)
BMI (kg/m^2)				
Mean (SD)	27.9 (± 5.28)	27.3 (± 4.61)	27.8 (± 5.70)	28.5 (5.70)
Min, Max	17.6, 42.6	17.6, 39.6	14.3, 42.9	16.8, 43.9
Education				
<= 12 years, N (%)	27 (41.5)	31 (49.2)	22 (35.5)	27 (45.0)

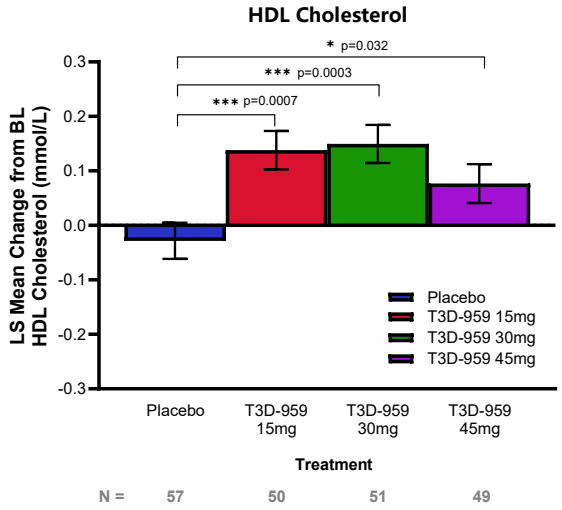
	Placebo (N=65)	T3D-959 15mg (N=63)	T3D-959 30mg (N=62)	T3D-959 45mg (N=60)
APOE4 Status				
Positive, N (%)	28 (44.4)	28 (44.4)	26 (41.9)	24 (40.0)
Concomitant AD Therapy				
Yes, N (%)	43 (66.2)	38 (60.3)	42 (67.7)	42 (70.0)
Screening MMSE				
Mean (SD)	19.7 (± 3.13)	20.6 (± 3.55)	20.6 (± 3.35)	21.3 (± 3.03)
Min, Max	14, 26	14, 26	14, 26	14, 26
Baseline ADAS-Cog				
Mean (SD)	19.8 (± 6.45)	19 (± 8.17)	21 (± 6.92)	18 (± 8.58)
Min, Max	6.0, 35.0	6.0, 47.0	7.0, 42.0	4.0, 49.0
HbA1c				
Pre-diabetes: 5.7% or higher, N (%)	42 (68.9)	32 (52.5)	32 (51.6)	38 (66.7)
Normal: less than 5.7%, N (%)	19 (31.1)	29 (47.5)	30 (48.4)	19 (33.3)
Aβ 42/40 Ratio				
High: 0.089 or higher, N (%)	36 (55.4)	37 (60.7)	40 (64.5)	32 (54.2)
pTau-217/ Non-pTau-217 Ratio				
High: 0.015 or higher, N (%)	29 (47.5)	34 (58.6)	36 (62.1)	30 (53.6)

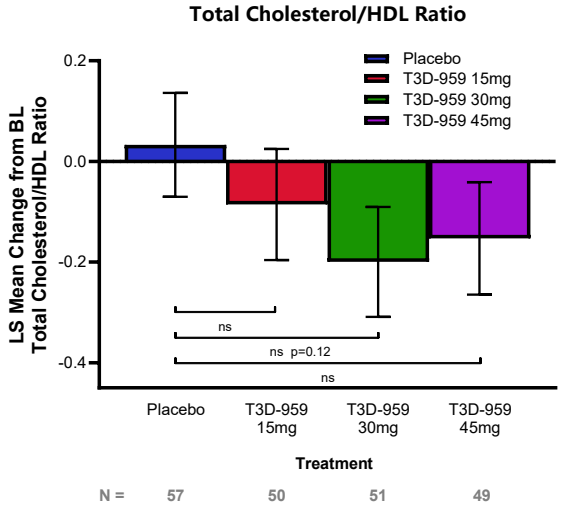
Mechanistic Proof of Target Engagement – Peripheral







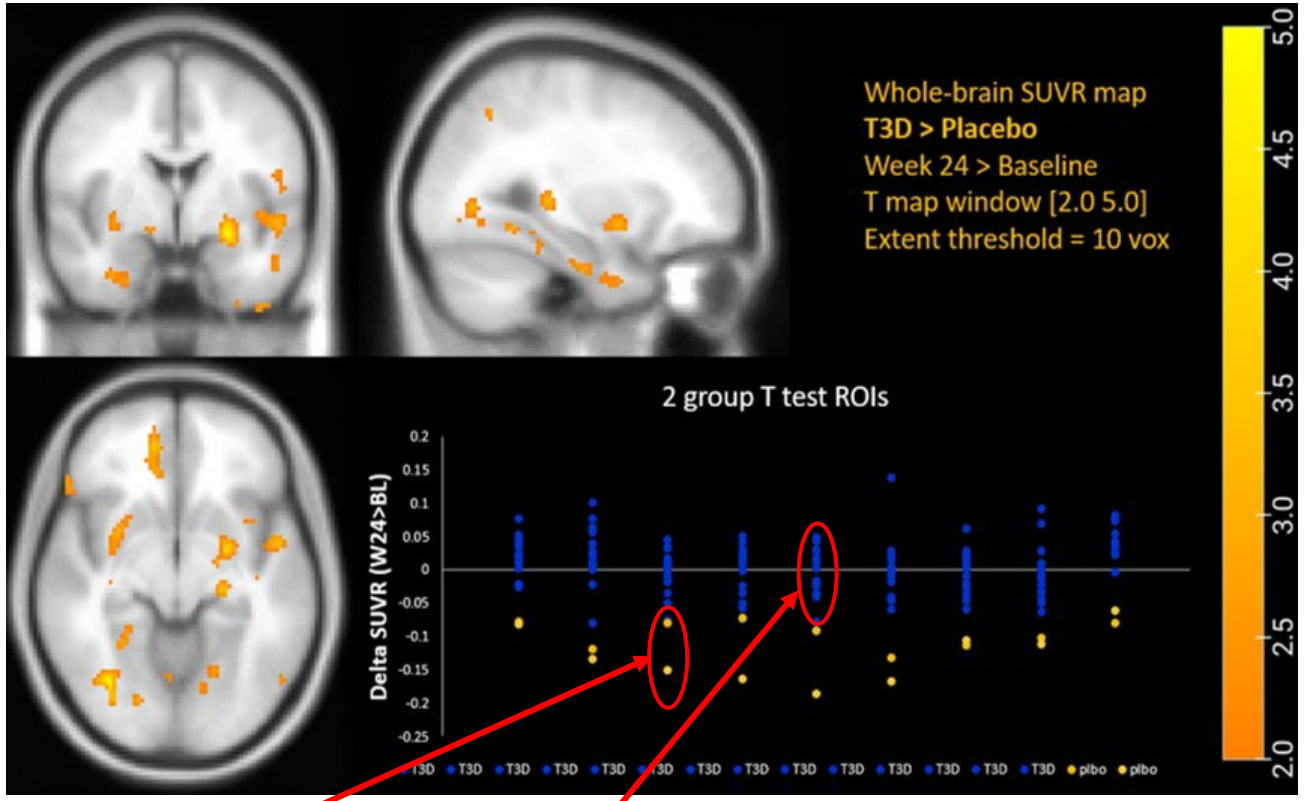




1. Glucose Metabolism - Insulin Sensitization
2. Lipid Metabolism - Improving Dyslipidemia
3. ↑ HDL and ↓ triglycerides supportive of blood brain barrier integrity
4. Target Engagement Supporting 30mg Efficacious Dose
5. PPAR delta and gamma ‘dialed in’ to the right degree at 30mg

Mechanistic Proof of Target Engagement – Central (Brain Glucose Metabolism via FDG-PET – Voxel-Wise Analysis)

Significant Changes from BL in Brain Regions Including:	
ROI1	L parahippocampal
ROI2	L putamen
ROI3	L DLPFC
ROI4	L DLPFC
ROI5	R OFC
ROI6	R aPFC
ROI7	R hippocampus
ROI8	R visual assoc
ROI9	Brainstem



1. Small sub-study with 2 on placebo and 14 on drug
2. Even with small N, significant evidence of a treatment effect with improved brain glucose metabolism in T3D-959 vs. placebo

Safety

- 250 randomized subjects representing > 5,500 patient dosing weeks
- 265 AEs across 97 subjects
- 13 minor drug-related AEs and 4 placebo-related AEs across 12 subjects (drug-related: diarrhea 4x, edema peripheral 2x, back pain, flatulence, flushing, headache, irritability, muscle spasms, pruritis)
- No drug-related SAEs
- 13 drug-unrelated SAEs (seizure, hip fracture, arm fracture, vertigo/loss of peripheral vision, giant cell arteritis, bladder cancer/postop complications, Bell's palsy, colitis, hypotension/fall/rib fracture, end stage dementia, heart attack, transient ischemic attack, septic shock/acute hepatic encephalopathy/MRSA bacteremia)
- 1 drug-unrelated death (end stage dementia)
- 1 dropout due to drug-related AE (mild edema peripheral)
- No high frequency of any AE type

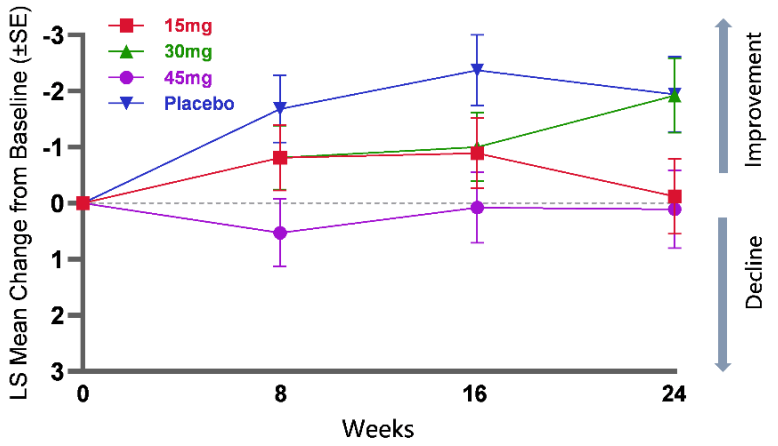
Safety

Number (%) of subjects with adverse events

	T3D-959 15mg (N=63) n (%)	T3D-959 30mg (N=62) n (%)	T3D-959 45 mg (N=60) n (%)	Placebo (N=65) n (%)
Any adverse event	21 (33.3)	26 (41.9)	22 (36.7)	28 (43.1)
Adverse event related to drug or placebo	2 (3.2)	2 (3.2)	6 (10.0)	2 (3.1)
Serious adverse event	1 (1.6)	4 (6.5)	3 (5.0)	3 (4.6)
Adverse event resulting in discontinuation	1 (1.6)	1 (1.6)	1 (1.7)	3 (4.6)
Death	1 (1.6)	0	0	0
Adverse events with incidence ≥ 3% in any group				
COVID-19	5 (7.9)	7 (11.3)	4 (6.7)	9 (13.8)
Diarrhea	2 (3.2)	4 (6.5)	3 (5.0)	2 (3.1)
Urinary tract infection	2 (3.2)	2 (3.2)	3 (5.0)	3 (4.6)
Headache	1 (1.6)	1 (1.6)	3 (5.0)	2 (3.1)
Upper respiratory tract infection	3 (4.8)	0	0	1 (1.5)
Fall	2 (3.2)	1 (1.6)	0	3 (4.6)
Oedema peripheral	0	2 (3.2)	2 (3.3)	0
Back pain	1 (1.6)	0	2 (3.3)	0
Urinary incontinence	1 (1.6)	0	0	2 (3.1)
Anaemia	0	2 (3.2)	0	0
Osteoarthritis	0	2 (3.2)	0	0

Primary and Secondary Neuropsychological Endpoints: ADAS-Cog11, ADCS-CGIC, and DSCT

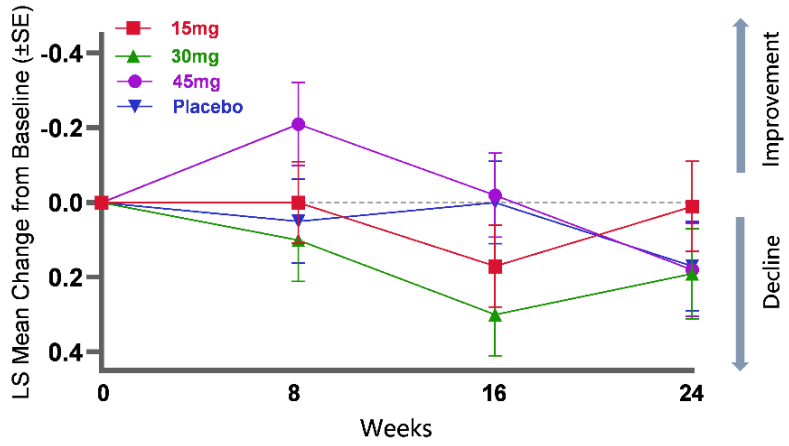
ADAS-Cog11



15mg	63	58	55	54
30mg	62	58	55	53
45mg	59	56	54	49
Placebo	65	59	55	57

ADAS-Cog11= Alzheimer's Disease Assessment Scale - Cognitive Subscale 11 item; LS = Least Squares; SE = Standard Error

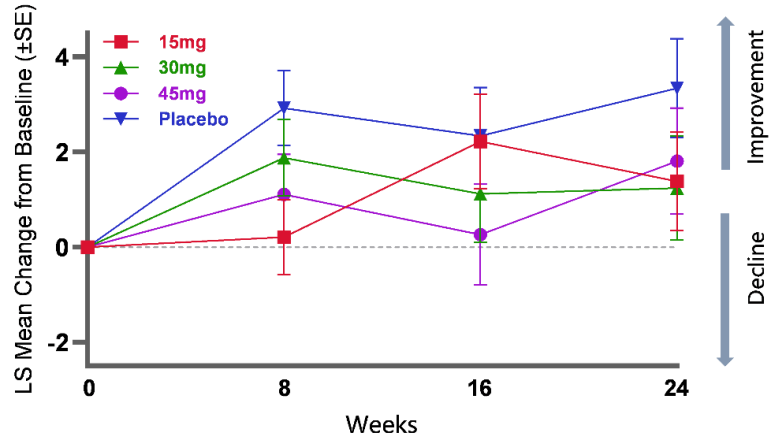
ADCS-CGIC



15mg	58	54	53	
30mg	57	53	53	
45mg	57	53	52	
Placebo	57	56	58	

ADCS-CGIC = Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change; LS = Least Squares; SE = Standard Error

DSCT



15mg	62	57	55	54
30mg	58	54	52	49
45mg	55	51	49	48
Placebo	60	58	52	55

DSCT= Digit Symbol Coding Test; LS = Least Squares; SE = Standard Error

1. Unexpected Placebo Response on the ADAS-Cog11 and DSCT
2. No improvement on the ADCS-CGIC

Baseline pTau-217/Non-pTau-217 Ratio as Diagnostic Marker

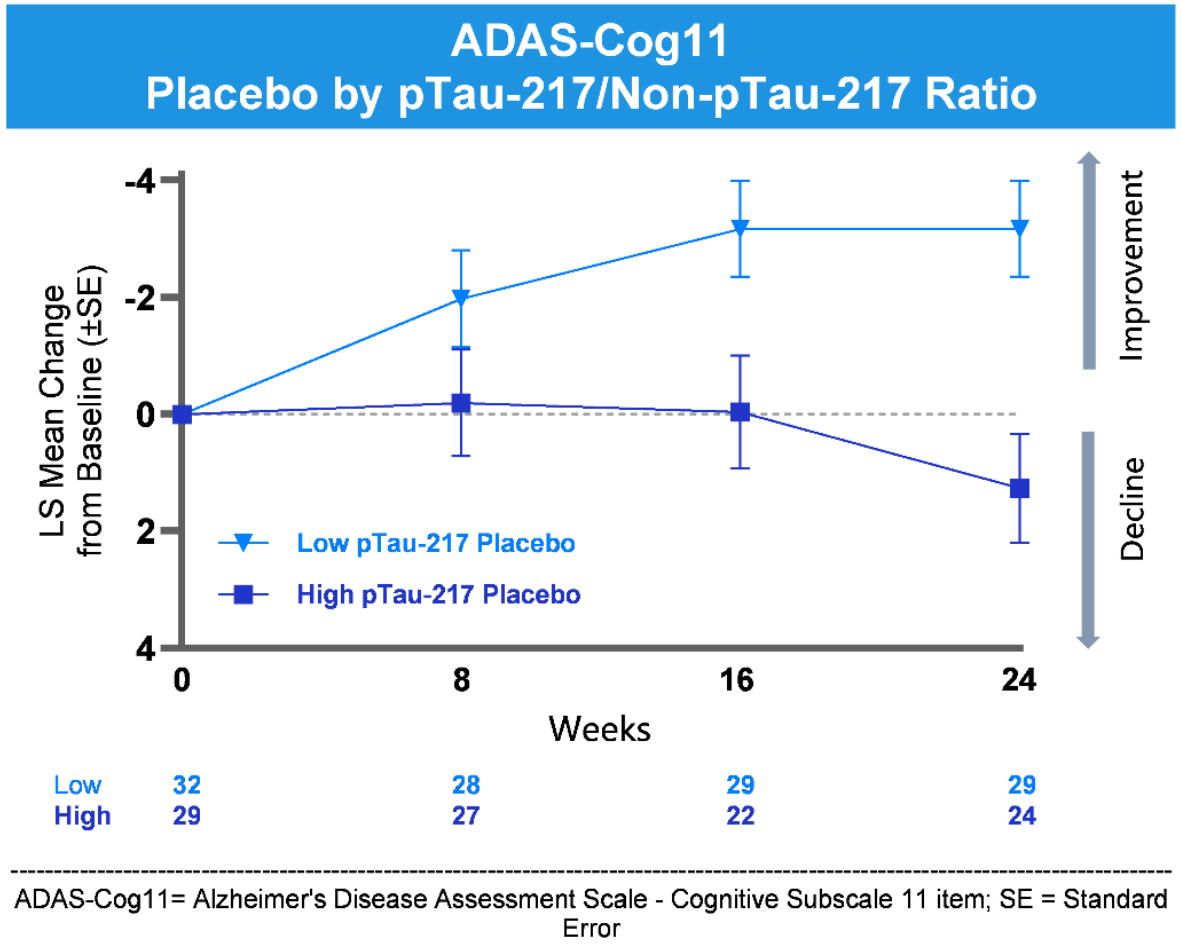
1. Baseline pTau-217/Non-pTau-217 ratio* is a marker of AD pathology
2. When added to the MMRM models of the primary endpoints, baseline pTau-217 ratio is the most significant covariate ($P < 0.0001$)
3. Follow-up subgroup analyses at C_2N-recommended cutoff of 0.015 (Low <0.015; High ≥0.015)
4. Subgroups look extremely different in their baseline characteristics

	Low pTau-217 Ratio	High pTau-217 Ratio
Enrolled	104 (44.6%)	129 (55.4%)
Female	73 (70.2%)	74 (57.4%)
Age	70.6 (± 7.55)	74.7 (± 7.88)
Hispanic/Latino	82 (78.8%)	42 (32.6%)
Education <= 12 years	59 (56.7%)	41 (31.8%)
MMSE	21.8 (± 2.5)	19.5 (± 3.5)
ADAS-Cog	16.8 (± 5.3)	21.6 (± 8.5)
APOE4 Positive	17 (16.3%)	78 (60.5%)
APS High	24 (23.1%)	102 (79.1%)
Concomitant AD Therapy	64 (61.5%)	86 (66.7%)
HbA1c Prediabetes	67 (64.4%)	68 (52.7%)
pTau-217 Ratio	0.007 (± 0.0063)	0.0445 (0.022)

Continuous variables are mean ± standard deviation

*pTau-217/Non-pTau-217 ratio based on C_2N CLIA assay V1.0

Baseline pTau-217/Non-pTau-217 Ratio Explains Placebo Effect



ADAS-Cog11= Alzheimer's Disease Assessment Scale - Cognitive Subscale 11 item; SE = Standard Error

Placebo by Baseline p-Tau-217/Non-p-Tau-217 Ratio – Mean Changes from Baseline across Neuropsychological Tests

ADAS-Cog

- Low pTau-217: 3.17-point improvement
- High pTau-217: 1.27-point decline

CGIC

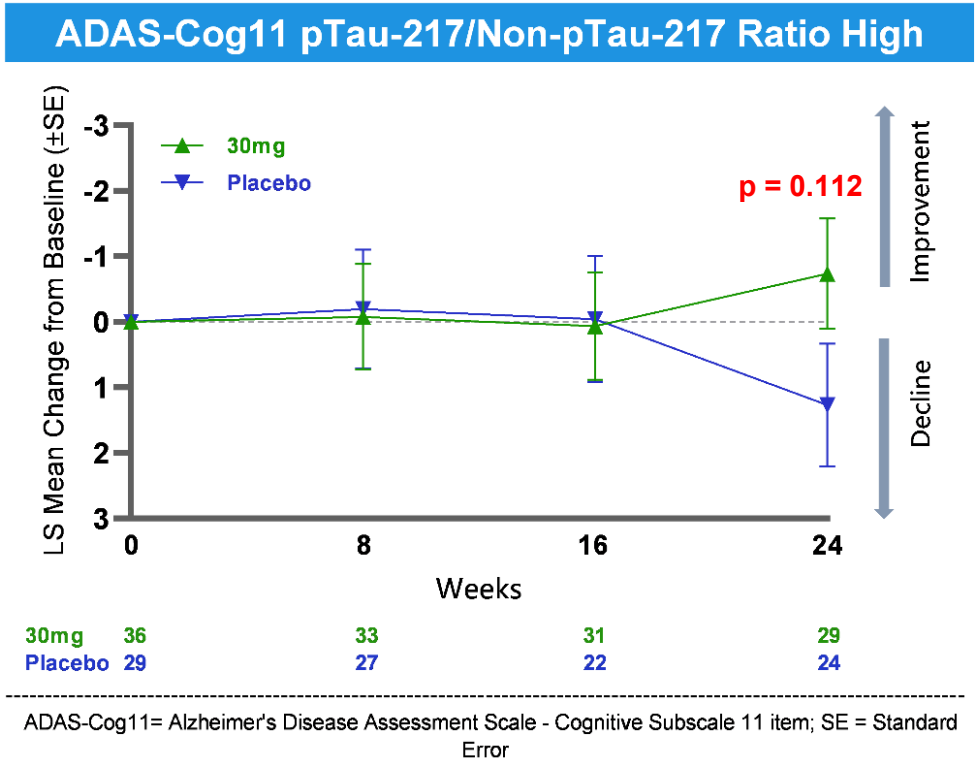
- Low pTau-217: 0.30-point improvement
- High pTau-217: 0.64-point decline

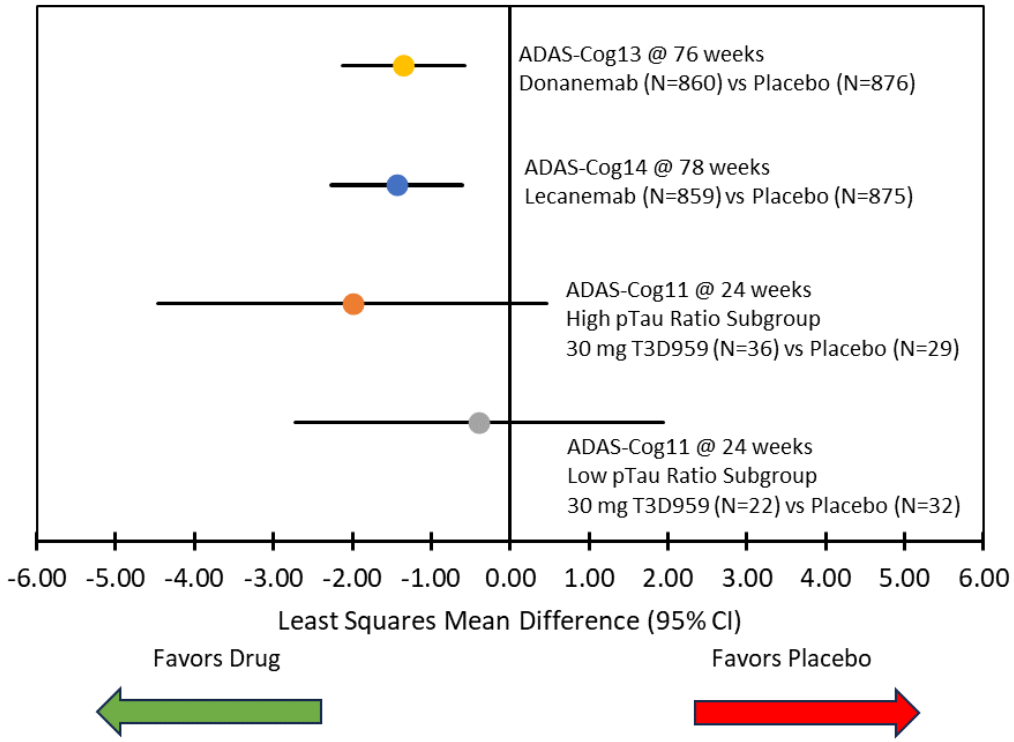
DSCT

- Low pTau-217: 5.49-point improvement
- High pTau-217: 1.24-point decline

1. Placebo subjects with low Baseline pTau-217 improved on all neuropsychological tests
2. Placebo subjects with high Baseline pTau-217 declined as expected. Suggests that this may be the more appropriate AD population for these endpoints

ADAS-Cog11 by pTau-217/Non-pTau-217 High Ratio





High pTau-217 ratio subgroup ADAS-Cog11:

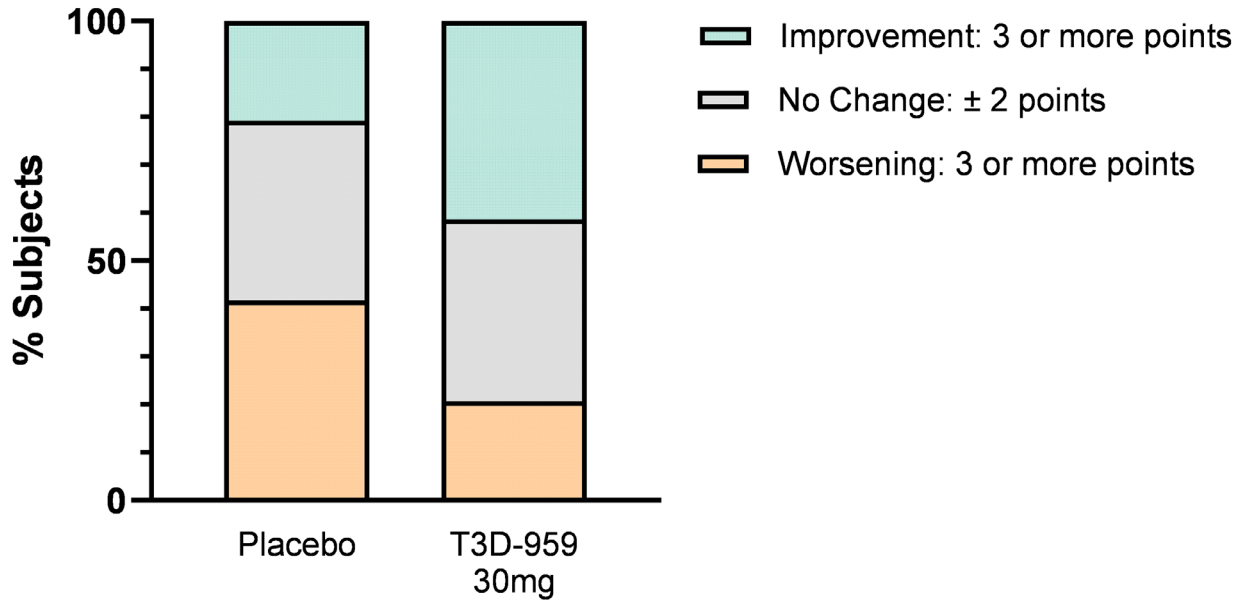
1. Clinical benefit of 2 points on the ADAS-Cog11 T3D-959 30mg vs. placebo in the high pTau-217 ratio subgroup
2. T3D-959 30mg at 24 weeks effect size equivalent or better than lecanemab and donanemab at 76-78 weeks

ADAS-Cog11 Clinically Meaningful Change
High pTau-217/Non-pTau-217 Ratio Subgroup

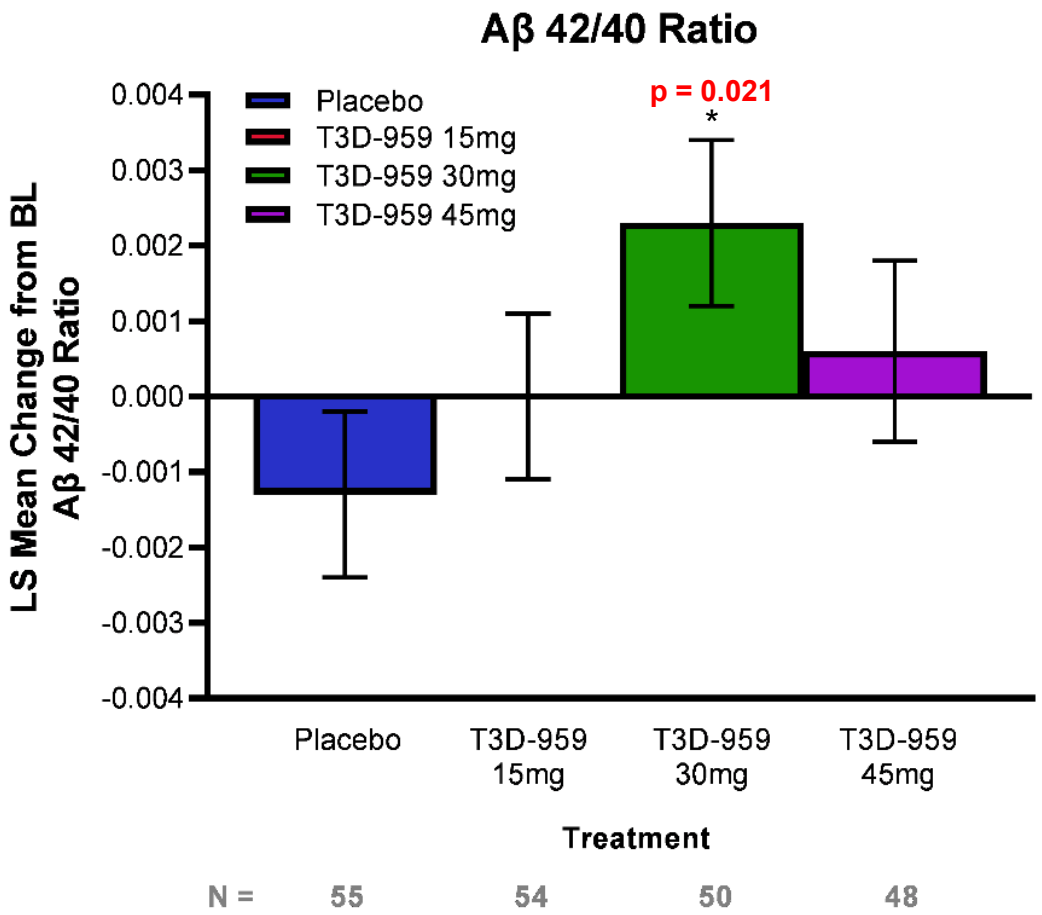
T3D959 30mg dose group experienced less clinically meaningful worsening AND more clinically meaningful improvement than placebo

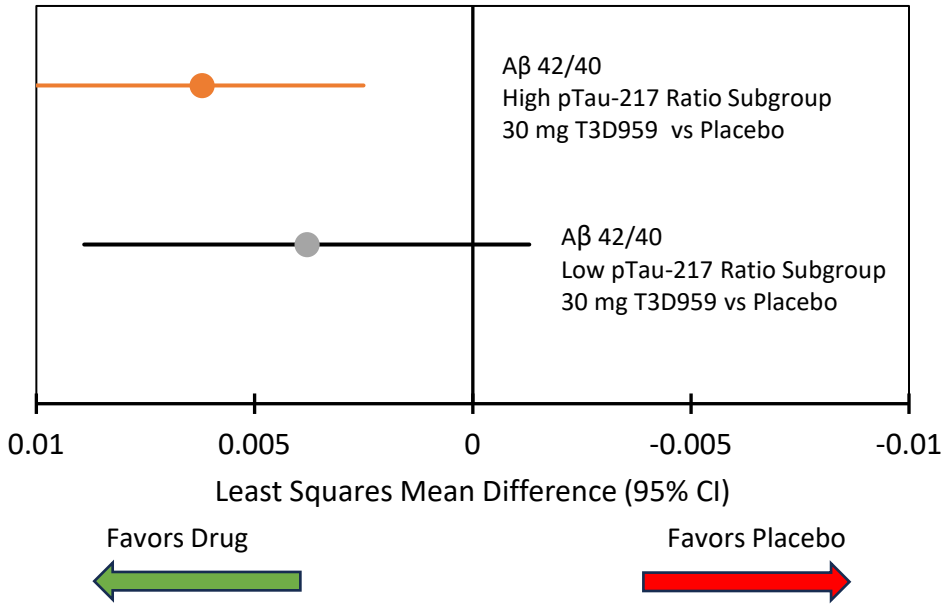
	T3D-959 15mg	T3D-959 30mg	T3D-959 45mg	Placebo
Improvement	6 (20.7)	12 (41.4)	4 (16.0)	5 (20.8)
No Change	11 (37.9)	11 (37.9)	10 (40.0)	9 (37.5)
Worsening	12 (41.4)	6 (20.7)	11 (44.0)	10 (41.7)
P-value	0.99	**0.059**	0.73	

P-value is based on CMH row mean scores test.



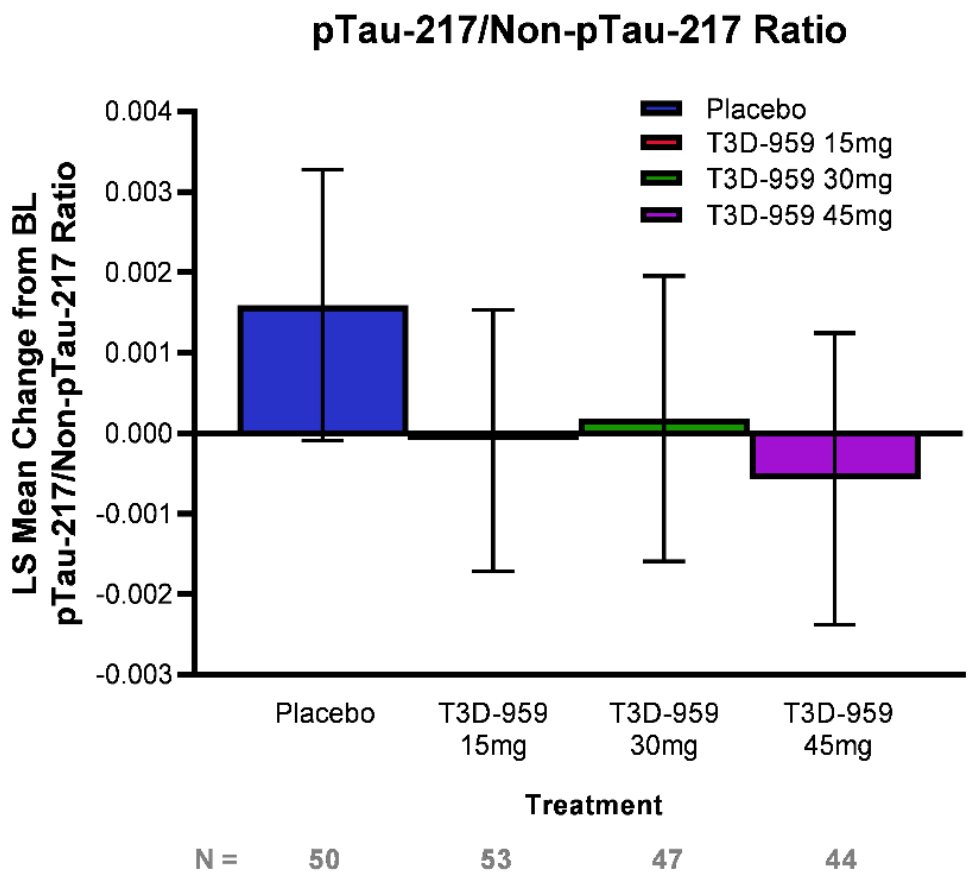
Secondary Endpoint: Plasma Amyloid Beta 42/40 Ratio

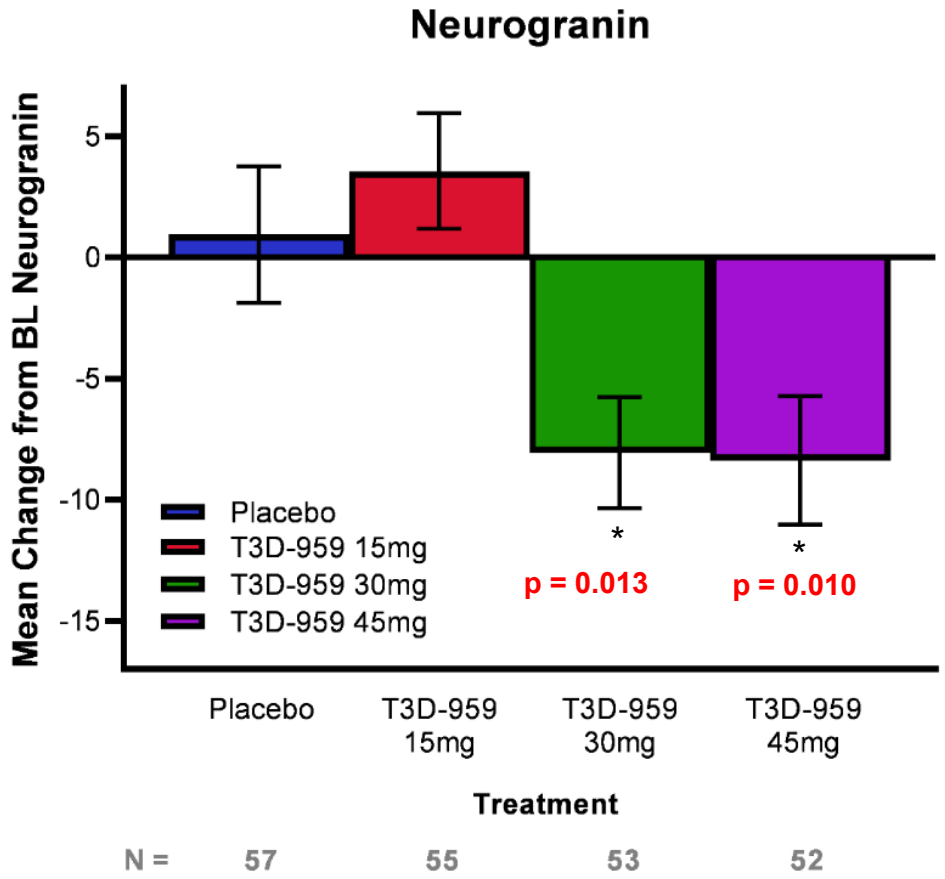




1. Significant Improvement at 30mg
2. Greater improvement in high pTau-217 ratio subgroup

Exploratory: A/T/N Markers





1. pTau-217 ratio shows disease progression in placebos; possibly halted with drug treatment
2. Neurogranin, a marker of neurodegeneration associated with synaptic loss, shows significant improvement with 30mg and 45mg drug treatment

Exploratory Plasma Biomarkers (LC-MS measures) Summary

Metabolomic Biomarker (Plasma) With Significant Improvement	AD Pathology
Branched Chain Amino Acids	Neuron Dysfunction
Neutral Lipids	Neurodegeneration
Ceramides	Neurodegeneration
Collagen Re-Modeling / Turnover	Neurodegeneration
Acyl Cholines	Neurotransmitter Deficits
Acyl Carnitines	Mitochondria Dysfunction
Lysophospholipids	Inflammation
Lipid Inflammatory Mediators	Inflammation
Anti-Oxidant Metabolites	Oxidative Stress

Proteomic Biomarker (Plasma) With Significant Improvement	AD Pathology
IL-18	Inflammation
BDNF	Neurodegeneration; Progression-dependent changes
von Willebrand Factor	Endothelial cell injury (decrease could be protective against ARIA)
Transthyretin (trend level)	Amyloid plaque formation, vascular defects (increase could be protective against ARIA)
Gelsolin	Amyloid plaque formation, oxidative stress, neurodegeneration
Hemoglobin Subunit Beta	Oxidative stress, neurodegeneration
Ficolin-2	Brain atrophy, neurodegeneration, insulin resistance, inflammation
Adiponectin	Aβ deposition, tau phosphorylation, oxidative stress, inflammation, insulin resistance
Apolipoprotein C-III	Inflammation, aberrant lipid metabolism (triglycerides)
Apolipoprotein A-I	Aberrant lipide metabolism (HDL)

1. Modification of Multiple Pathophysiologies of Alzheimer's Disease
2. Normal Metabolic Pathways Being Restored

T3D Therapeutics PIONEER Results Summary

- Clinical evidence of:
  1. A modification of multiple AD pathologies associated with amyloid plaque burden
  2. A reduction in amyloid plaque burden is suggested from biomarker data
  3. Improvement in cognition
  4. High safety advantage over marketed therapies

- A high plasma pTau-217 ratio marker of AD pathology likely defines an AD population responsive to T3D-959 therapy.

- Biomarker results show T3D-959 to improve:
  1. All three A/T/(N) AD diagnostic criteria [Amyloid/Tau/Neurodegeneration)]
  2. Inflammation
  3. Insulin resistance
  4. Dysfunctional metabolism (glucose and lipid)

- Plasma biomarker and neuropsychological test results identify a 30mg q.d. dose as providing optimal safety and efficacy for further investigation.

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